IDENTIFICATION AND CHARACTERIZATION OF HIGH-AFFINITY SOMATOSTATIN - SSTR2 RECEPTOR SUBTYPES ON ESTABLISHED TUMORS AND TUMOR CELL LINES.

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Somatostatin (SRIF) analogues are potent inhibitors of *in vitro* tumor cell proliferation and effective antiproliferative peptides against *in vivo* tumor xenografts (e.g., lung, prostate, pancreas, and breast tumors). The antitumor activity of SRIF peptides appears to be mediated via high-affinity receptors and may involve, secondarily, the direct suppression of tumor growth or the inhibition of local growth factor secretion. Recent receptor cloning studies have demonstrated the presence of at least three SRIF receptor subtypes, SSTR1, SSTR2, and SSTR3 in mammalian tissues. Although the relationship of the subtypes to the antiproliferative activity of SRIF peptides is not known, some of the most effective SRIF antitumor peptides (e.g., BIM-23014, D-Nal-cyclo[Cys-Try-D-Trp-Lys-Val-Cys]-Thr-NH_2) show a high degree of specificity for the SSTR2 receptor. Clearly, a knowledge of the SRIF receptor subtype present on tumor samples would lead to a more rational approach to application of SRIF peptides for the treatment of cancer. Accordingly, SSTR2 receptor sites on various *in vitro* tumor cell lines and *in vivo*-maintained transplantable human and rodent tumors were characterized using the SSTR2-selective radioligand [^{125}I]MK-678. [^{125}I]MK-678 binding was saturable, selective for SSTR2-specific SRIF peptides, and variably expressed in several tumors and tumor cell lines.

Tumor	*SSTR2 Receptor Conc. (fmol/mg protein)*
pancreas AR42J (rat)	2650
small cell lung carcinoma NCI-H69 (human)	650
small cell lung carcinoma NCI-H345 (human)	215
prostate R3327 (rat)	55
non-small cell lung carcinoma A 549 (human)	13
breast MDA-MB-231 (human)	12

Interestingly, the SSTR2 receptor densities in the rat AR42J pancreas and R3327 prostate were significantly higher than that observed in the respective normal tissues (e.g., rat pancreas = 440 fmol/mg protein; rat prostate = no detectable binding) indicating a selective enrichment in the neoplastic tissues. These results confirm earlier receptor studies with nonselective SRIF radioligands and suggest that the SSTR2 receptor subtype may be selectively overexpressed in certain tumors as an endogenous compensatory mechanism to retard tumor cell proliferation and growth. Secondly, this phenomenon may be a marker for SRIF-sensitive tumors and explain the significant antitumor activity of SSTR2 specific peptides.

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